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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,974	02/21/2002	Joseph Rubinfeld	12636-263	2253
21971	7590	12/02/2004	EXAMINER	
WILSON SONSINI GOODRICH & ROSATI 650 PAGE MILL ROAD PALO ALTO, CA 943041050			MCINTOSH III, TRAVISS C	
			ART UNIT	PAPER NUMBER
			1623	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/081,974

**Applicant(s)**

RUBINFELD ET AL.

**Examiner**

Traviss C McIntosh

**Art Unit**

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-- **Th MAILING DATE of this communication appears n th cover sheet with the corresp ndenc addr ss --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-16, 18-21 and 25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-16, 18-21 and 25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)                        |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____   |

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### **DETAILED ACTION**

The Amendment filed September 1, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1-16 and 18-20 have been amended.

Claims 17 and 22-24 have been canceled.

Remarks drawn to rejections of Office Action mailed June 29, 2004 include:

103(a) rejection which has been overcome by applicant's amendments and arguments and has been withdrawn.

An action on the merits of claims 1-16, 18-21, and 25 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

#### ***Claim Rejections - 35 USC § 103***

Claims 1-16, 18-21, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernacki et al. ("In Vitro Antitumor Activity of 9-Nitro-Camptothecin as a Single Agent and in Combination with other Antitumor Drugs", Annals of the New York Academy of Sciences, vol 922, pp. 293-297, 2000), newly cited, in view of the combination of Rubinfeld (US Patent 6,191,119) and Achterrath (US Patent 6,403,569).

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Claim 1 is drawn to a method of treating cancer in a patient with p53 mutation comprising administering either 9-nitro-20(S)-camptothecin (9-NC) or 9-amino-20(S)-camptothecin (9-AC) 1 day before or after administering 5-fluorouracil (5-FU), wherein the 5-FU is not present in the subject. Claims 2-6 provide that the 20(S)-camptothecin is administered at least 1-5 days before the 5-FU, respectively. Claims 7-11 provide that the 20(S)-camptothecin is administered at least 1, 2, 3, 4, or 5-90 days before the 5-FU. Claims 12-16 provide that the 20(S)-camptothecin is administered at least 1, 2, 3, 4, or 5 days after the 5-FU. Claims 18-20 provide that the 20(S)-camptothecin is administered between 2, 3, or 4 to 90 days before or after the 5-FU is administered, and wherein the 20(S) camptothecin is administered within 2, 3, or 4 days of when the 5-FU is administered. Claims 21 and 25 provide various cancers which the patients have.

Bernacki et al. teaches that sequential combinations of 9-NC followed by 5-FU 24 hours later, appeared to be highly synergistic at high dose-effect levels. Bernacki et al. then suggest that sequential drug administration may be more efficacious at high effect level and that the order of drug addition is very important. Bernacki et al. additionally teach that the sequential combination of 9-NC (or other camptothecin analogues) followed by 5-FU has potential for the treatment of cancer in man (see abstract). What is not taught is the specific method practiced on patients with p53 mutations, nor some of the various alternative time requirements for the sequential therapy as claimed.

Rubinfeld teaches of methods for treating cancer comprising the use of combination therapy by coadministering to the patient a 20(S)-camptothecin (including 9-nitro-20(S)-

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camptothecin) in combination with for example, a synergistic antimetabolite, such as 5-fluorouracil (column 2, lines 37-67). It is noted that Rubinfeld defines coadministration to mean the administration of more than one therapeutic in the course of coordinated treatment to achieve clinical outcome, such coadministration may also be coextensive, that is, occurring during overlapping periods of time (column 5, lines 54-62).

What is not taught by Rubinfeld is to specifically use 5-fluorouracil, nor to allow for at least 1 day between the administration of the 5-fluorouracil and the 20(S)-camptothecin. Moreover, it is noted that while Rubinfeld does not specifically acknowledge the 1 day between the administration of the active agents, they do indeed recognize the alternative as an option, wherein they state that “such coadministration *may also be*, that is, occurring during overlapping periods of time”. This clearly sets forth that the coadministration may occur during overlapping periods of time, as well as during non-overlapping periods of time.

Achterrath teaches a method of treating cancer comprising administering at least one camptothecin derivative in combination with 5-fluorouracil (column 1, lines 8-15).

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the methods of the prior art and obtain the methods as claimed in the instant application with these references before them. Bernacki et al. clearly teach that 9-NC and 5-FU in a sequential combination has potential for the treatment of cancer in man (see results and discussion). Rubinfeld and Achterrath teach the use of 20(S)-camptothecins in combination therapy with 5-fluorouracil in treating cancers. Moreover, the prior art teaches of the synergistic effects of the sequential therapy (see Bernacki) and that the active agents may be administered in delayed release forms which may delay their release from about 1 hour to about 6 months (see

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'119, column 7, lines 36-39). Modifying the prior art methods and optimizing the time frames required between the active agents administration is seen to require nothing more than routine skill in the art, and one of ordinary skill in the art would be appraised of methods of determining the optimum time frames for that art recognized active agents to be administered.

The sequential therapy using 9-NC and 5-FU is known in the art. Moreover, the sequential therapy with at least 24 hours between administering the different agents is known in the art. Optimizing art recognized methods to determine the optimum time frame for the administration of the individual agents is seen to be well within the skill of one of skill in the art.

Applicant's arguments with respect to claims 1-16, 18-21, 23, and 25 have been considered but are moot in view of the new ground(s) of rejection.

### ***Conclusion***

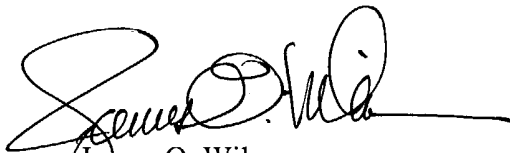
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III  
November 13, 2004



James O. Wilson  
Art Unit 1623  
Supervisory Patent Examiner